(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/73307 A3

(51) International Patent Classification[7]: C07D 473/06. A61K 31/505, A61P 11/06

(21) International Application Number: PCT/US00/15233

(22) International Filing Date: 1 June 2000 (01.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/136,898	1 June 1999 (01.06.1999)	US
60/136,900	1 June 1999 (01.06.1999)	US
60/151,875	31 August 1999 (31.08.1999)	US
09/505,504	17 February 2000 (17.02.2000)	US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report: 31 May 2001

(48) Date of publication of this corrected version: 28 February 2002

(15) Information about Correction: see PCT Gazette No. 09/2002 of 28 February 2002, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/73307 A3

(54) Title: SUBSTITUTED 8-PHENYLXANTHINES USEFUL AS ANTAGONISTS OF A_{2B} ADENOSINE RECEPTORS

(57) Abstract: The present invention provides compounds and pharmaceutical compositions that are selective antagonists of A_{2B} adenosine receptors (ARs). These compounds and compositions are useful as pharmaceutical agents.

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Published:
— *With international search report.*

(88) Date of publication of the international search report:
31 May 2001

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INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/US 00/15233

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D473/06 A61K31/505 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	US 4 696 932 A (JACOBSON KENNETH A ET AL) 29 September 1987 (1987-09-29) column 3 ---	1-37
X,Y	JACOBSON ET AL.: "Functionalized congeners of 1,3-dialkylxanthines..." J.MED.CHEM., vol. 28, no. 9, 1985, pages 1334-1340, XP000942532 table I --- -/--	1-37

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 2000	28/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 00/15233

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	CHEMICAL ABSTRACTS, vol. 109, no. 25, 19 December 1988 (1988-12-19) Columbus, Ohio, US; abstract no. 221931, JACOBSON, KENNETH A. ET AL: "8-Substituted xanthines as antagonists at A1- and A2-adenosine receptors" XP002151161 abstract & BIOCHEM. PHARMACOL. (1988), 37(19), 3653-61 ,	1-37
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X,Y	BRACKETT ET AL.: "Functional characterization of the A2b adenosine ..." BIOCHEMICAL PHARMACOLOGY, vol. 47, no. 5, 1994, pages 801-814, XP000942545 table 3	1-37
P,X, Y	WO 99 42093 A (LINDEN JOEL M ;UNIV VIRGINIA (US)) 26 August 1999 (1999-08-26) claim 10	1-37
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INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/US 00/15233

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

Inter. ...nal Application No
PCT/US 00/15233

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PCT

International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61K 31/70, A61K 48/00, A61K 49/00, C07H 21/00, C12N 15/63

A1

(11) International Publication Number: WO 00/51621

(43) International Publication Date: 08 September 2000 (08.09.2000)

(21) International Application Number: PCT/US00/05643

(22) International Filing Date: 02 March 2000 (02.03.2000)

(30) Priority Data:
60/122,950 05 March 1999 (05.03.1999) US

(60) Parent Application or Grant
EPIGENESIS PHARMACEUTICALS, INC. [/]; (). NYCE, Jonathan, W. [/]; (). NYCE, Jonathan, W. [/]; (). AMZEL, Viviana ; ().

Published

(54) Title: METHOD FOR VALIDATING/INVALIDATING TARGET(S) AND PATHWAYS

(54) Titre: PROCEDE DE VALIDATION/D'INVALIDATION DE CIBLES ET DES VOIES

(57) Abstract

A method of determining the existence of a correlation between a function of a disease or condition and a gene or mRNA encoding a target polypeptide suspected of being associated with a disease or condition, comprises obtaining oligonucleotides (oligos) consisting of up to about 15 % adenosine (A), preferably having no adenosine content, and which is anti-sense to a target selected from the group consisting of target genes and their corresponding mRNAs, genomic and mRNA flanking regions selected from the group consisting of 3' and 5' intron-exon borders and the juxta-section between coding and non-coding regions, and all mRNA segments encoding polypeptides associated with a pre-selected disease or condition; selecting amongst the oligos one that significantly inhibits or ablates expression of the polypeptide encoded by the mRNA upon in vitro hybridization to the target mRNA; administering to a subject an amount of the selected oligo effective for in vivo hybridization to the target mRNA; and assessing a subject=s function that is associated with the disease or condition before and after administration of the oligo; wherein a change in the function=s value greater than about 70 % indicates a positive correlation, between about 40 and about 70 % a possible correlation, and below about 30 % a lack of correlation. The present method preferably administers the oligos in situ where the target is located, e.g. into the subject=s respiration when validating targets associated with malignant and other pulmonary and respiratory functions, so that the agent has direct access to the lungs. Alternatively, such desAdenosine oligos may be delivered directly to the CNS or other organs, tissues and organ systems, by means of known delivery formulations.

(57) Abrégé

La présente invention concerne un procédé pour déterminer l'existence d'une corrélation entre une fonction et une affection ou un état pathologique et un gène ou un ARNm codant un polypeptide cible présumé d'être associé à une affection ou à une condition, qui consiste à: disposer d'oligonucléotides (oligos) comprenant au plus environ 15 % d'adénosine (A), de préférence ne contenant pas d'adénosine, et qui est un antisens à la cible sélectionnée dans le groupe constitué des gènes cibles et leurs ARNm correspondants, les régions génomiques et les régions flanquantes de l'ARNm sélectionnées dans le groupe constitué des frontières intron-exon 3' et 5' et la section de juxtaposition entre les régions codantes et non codantes, et tous les segments de l'ARNm codant des polypeptides associés à une affection ou à une condition prédéterminée; sélectionner parmi les oligos un qui présente une activité d'inhibition ou d'ablation notable vis-à-vis de l'expression d'un polypeptide codé par le ARNm lors d'une hybridation in vitro à l'ARNm cible; administrer à un sujet une quantité efficace d'oligo sélectionné pour une hybridation in vivo à l'ARNm cible; et évaluer une fonction sujet=s qui est associée à l'affection ou la condition avant et après l'administration de l'oligo; dans lequel une modification dans la valeur de la fonction=s supérieure à environ 70 % signifie une corrélation positive, entre environ 40 et environ 70 % une corrélation possible, et inférieure à 30 % un manque de corrélation. De préférence, ledit procédé effectue l'administration des oligos in situ où la cible est localisée, par exemple dans le système respiratoire du sujet=s lors d'une validation de cibles associées à des fonctions malignes et autres fonctions pulmonaires et respiratoires, de sorte que l'agent peut accéder directement aux poumons. Alternativement, de telles adénosines (desA) peuvent être délivrées directement au système central nerveux ou à d'autres organes, systèmes de tissus ou d'organes, au moyen de formulations d'administration connues.